Automated noninvasive classification of renal cancer on multiphase CT

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Purpose: To explore the added value of the shape of renal lesions for classifying renal neoplasms. To investigate the potential of computer-aided analysis of contrast-enhanced computed-tomography (CT) to quantify and classify renal lesions.

Methods: A computer-aided clinical tool based on adaptive level sets was employed to analyze 125 renal lesions from contrast-enhanced abdominal CT studies of 43 patients. There were 47 cysts and 78 neoplasms: 22 Von Hippel-Lindau (VHL), 16 Birt-Hogg-Dube (BHD), 19 hereditary papillary renal carcinomas (HPRC), and 21 hereditary leiomyomatosis and renal cell cancers (HLRCC). The technique quantified the three-dimensional size and enhancement of lesions. Inpatient and interphase registration facilitated the study of lesion serial enhancement. The histograms of curvature-related features were used to classify the lesion types. The areas under the curve (AUC) were calculated for receiver operating characteristic curves.

Results: Tumors were robustly segmented with 0.80 overlap (0.98 correlation) between manual and semi-automated quantifications. The method further identified morphological discrepancies between the types of lesions. The classification based on lesion appearance, enhancement and morphology between cysts and cancers showed AUC = 0.98; for BHD + VHL (solid cancers) vs. HPRC + HLRCC AUC = 0.99; for VHL vs. BHD AUC = 0.82; and for HPRC vs. HLRCC AUC = 0.84. All semi-automated classifications were statistically significant ($p < 0.05$) and superior to the analyses based solely on serial enhancement.

Conclusions: The computer-aided clinical tool allowed the accurate quantification of cystic, solid, and mixed renal tumors. Cancer types were classified into four categories using their shape and enhancement. Comprehensive imaging biomarkers of renal neoplasms on abdominal CT may facilitate their noninvasive classification, guide clinical management, and monitor responses to drugs or interventions. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3633898]

Key words: kidney, cancer, segmentation, classification, computer-aided diagnosis

I. INTRODUCTION

A quarter of a million people in the USA are living with renal cancer and their number increases by over 50,000 yearly.¹ Given the aggressive nature of certain types of renal cancers and the rapid drop of survival rates with the advancement of disease, the robust quantification and correct classification of renal neoplasms is essential for their prompt and responsive management.²⁻⁴ This study investigates the potential of noninvasive imaging biomarkers to quantify and classify renal lesions.

Contrast-enhanced computed-tomography (CT) has proven exceptionally useful to cancer diagnosis due to the ability to differentiate tumors from healthy renal tissue.^{5,6} The enhancement and homogeneity of tumors are crucial indicators of malignancy,⁶⁻⁸ but a reliable diagnosis remains challenging without performing biopsy. Noninvasive techniques

to advance the strategies for cancer treatment will rely on a combination of adequate perception of the underlying biological mechanisms⁹ and imaging biomarkers.

In a typical clinical scenario, tumors size and enhancement are evaluated manually. Size indicates cancer evolution, response to treatment and the necessity of surgery. The enhancement of a lesion is the primary biomarker used to classify it. While size is approximated by a two-dimensional (2D) measurement of the longest axis in a CT projection (typically the axial view), the intensity is estimated from 2D circular regions in the center of a tumor. Manual measurements show high intra- and interoperator variability. In this context, computer-assisted radiology can improve the diagnosis of renal tumors by 3D quantifications of size, enhancement and morphology from image analysis.

Commonly, renal lesions appear visually spherical with smooth surfaces. However, details of their shape may be influenced locally by the position inside/on the kidney, the solidity, and vascularity of the tumor and the properties of the surrounding tissue. This study explores the added value of the shape of renal lesions as an important feature for determining renal cancer types.

Most work in computer-aided renal image analysis performed kidney segmentation.^{10–14} Notably, kidneys were segmented from contrast-enhanced CT in Refs. 16–18. However, the quantification and classification of renal tumors were seldom addressed. A marker-controlled watershed algorithm segmented kidneys and lesion in 2D images using three manual contours and granulometry.¹⁹ A homogeneous region growing from a seed point was presented in Ref. 20.

More often, tumors outside of the kidney were analyzed, especially in the liver,^{21–24} lungs,^{25–28} brain,^{29–31} breast,^{32–34} and colon.^{32,35} The majority of these papers address the segmentation of lesions. Machine learning classifiers using morphological features were used to distinguish between benign and malignant types.^{28,34–36} To our knowledge, no such classifiers or shape analysis were employed for renal lesions.

Statistical information of basic image descriptors, such as the edge and gradient, has shown promising results in computer vision research. Representative methods include the scale-invariant feature transform,³⁷ shape context,³⁸ and histograms of oriented gradient.³⁹ Methods such as the scale-invariant feature transform and shape context rely on key or edge points and in many medical imaging applications it is challenging to find distinct local structures to serve as markers. The histograms of oriented gradient does not require key points, although remains sensitive to image rotation.

Inspired by the histograms of oriented gradient, in this paper we propose a set of shape descriptors called histograms of curvature features (HCF) to describe renal lesions. HCF was previously used for colon polyp matching;⁴⁰ we employ it to classify renal tumors. HCF are rotation, translation and scale-invariant statistical descriptors that capture the intrinsic properties of objects, for example shape and texture, and can be readily combined with intensity and enhancement descriptors of lesions for an accurate classification from CT data.

We propose the semi-automated quantification and classification of renal lesions for the management of renal cancer. First, volumetric and enhancement noninvasive biomarkers of renal tumors are extracted from serial contrast-enhanced CT. Then, histograms combining curvature features and multiphase lesion intensity are used to classify the lesion types. We segment and classify benign cysts and four types of renal cancers (VHL, BHD, HPRC, and HLRCC). This is, to our knowledge, the first semi-automated method that quantifies and classifies renal tumors using lesion morphology and serial enhancement.

II. MATERIALS AND METHODS

II.A. Data and materials

This retrospective study follows HIPAA-compliance standards. The project was IRB approved and informed consent

Fig. 1. Multiphase abdominal 4D CT data of a patient with VHL. 2D slices of 3D volumes are shown (a) before contrast and (b) at PVP, when tumors are better distinguished from the renal parenchyma.

was waived. Contrast-enhanced CT data consisted of two serial acquisitions per patient: one before contrast administration and a second during the portal venous phase (PVP). Patients were injected with 130 ml of Isovue-300 and PVP data were obtained using fixed delays of 65–70s. The CT tube voltage was 120 kVp and the current was 240–350 mAs. Data were collected with 2 mm collimation using QX/i and Light-Speed Ultra [GE Healthcare] and MX 8000 [Philips Healthcare] scanners with four, 8 and 16 detectors respectively. Images were reconstructed with a matrix size of 512×512 pixels with sizes between 0.64 and 0.97 mm and 1 mm slice thickness. Figure 1 shows renal normal parenchyma and lesions in contrast-enhanced CT.

Data from 43 patients (86 CT scans) with renal tumors were analyzed: 22 males (mean age 47, range 25–77), 21 females (mean age 45, range 19–76). There were 125 tumors, including 47 benign cysts. Of the 78 cancers, 22 were Von Hippel-Lindau (VHL) disease (11 patients), 16 Birt-Hogg-Dubé (BHD) syndrome (12 patients), 19 hereditary papillary renal carcinoma (HPRC—5 patients), and 21 hereditary leiomyomatosis and renal cell cancer (HLRCC—15 patients).⁴¹ Examples of tumor appearance variability can be found in Fig. 2.

Each patient had a single type of cancer, but could also exhibit cysts. Diagnosis was confirmed on a patient-basis by genetic testing for germline mutation. Cysts and cancers were identified by radiological examination. Lesion diameter manually measured from axial CT varied from 0.53 to 4.33 cm. Twenty lesions (four of each type: cysts, VHL, BHD, HPRC, and HLRCC) were segmented manually by two observers (research fellows supervised by an experienced radiologist) for the validation of the segmentation.

II.B. Preprocessing

A diagram of the algorithm flow is presented in Fig. 3. Data from the two-phase scans were automatically aligned by the image position relative to the body using scanning information. Then, anisotropic diffusion⁴² reduced the image noise. Inpatient interphase 3D nonlinear registration corrected for abdominal motion between subsequent acquisitions⁴³ to allow measuring the lesions' CT values at every enhancement phase (Fig. 4).

FIG. 2. Examples of types of renal tumors as they appear at PVP. The intensity and homogeneity inside the lesion are indications used in diagnosis. These examples include small, large, cystic (lower intensity-enhancement), and solid (higher intensity/enhancement), homogeneous and heterogeneous tumors. A BHD tumor is shown in (a); in (b) and (f) there are homogeneous and heterogeneous VHL cancers; cysts can be found in (c) and (f); a HPRC lesion is shown in (d); and a small HLRCC cancer is presented in (e).

II.C. Segmentation/quantification

Lesions were segmented in the PVP image following the algorithm in Ref. 44 using a combination of fast marching and geodesic active contour level sets.^{45,46} The fast marching method initialized the segmentation expanding from a seed point provided by the user inside the lesion. Then, the geodesic active contour refined the segmentation. The sigmoid of the gradients (∇I) computed from the PVP image (I) supplied the edge image (I_e).

$$I_e = 1 - \frac{1}{1 + \exp\left[-\frac{\nabla I - (\alpha + \beta)}{3(\alpha - \beta)}\right]},$$

where α and β were adaptively computed from ∇I .⁴⁴ Initially, a spherical tumor model was used to extract knowledge about the tumor boundaries and texture. The model and parameters were automatically adapted to each tumor in an iterative fashion. Volumetric measurements of the tumors were computed and the lesions' CT values (HU number) were extracted on both PVP and noncontrast CT scans.

II.D. Classification

The classification of renal tumors was based on histograms that combine morphological, texture and multiphase

(4D) intensity features; it can be seen as a cascade of binary classifiers for a multiple classification problem (Fig. 5). First malignant and benign groups were separated. Another binary classifier divided VHL/BHD (high enhancement) and HPRC/HLRCC (low enhancement) cancers. Finally, each type of cancer was identified.

Intuitively, curvature measures the extent that a geometric object deviates from flat. For a two-dimensional isosurface embedded in R^3 , the intersection of the surface with a plane containing the normal and tangent vectors at a point on the surface is a plane curve and has a normal curvature. The maximum and minimum values of the normal curvature are called principal curvatures, k_1 and k_2 . The mean curvature is $k_{\text{mean}} = (k_1 + k_2)/2$. The Gaussian curvature is defined as $k_{\text{Gaussian}} = k_1 k_2$ and describes a surface as locally convex or saddle.⁴⁷ Additionally, shape index (SI) and curvedness (CV) also describe the shape of an object.^{36,48} For example, SI of a cup is 0, of a cap is 1, of a ridge is 0.75, and of a saddle is 0.5.

$$SI(p) = \frac{1}{2} - \frac{1}{\pi} \arctan \frac{k_1 + k_2}{k_1 - k_2},$$

$$CV(p) = \frac{1}{2} \sqrt{k_1^2 + k_2^2}.$$

Histograms of curvature features are a more complete statistical view of a lesion based on the set of combined

FIG. 3. Diagram of the algorithm flow. Multiphase (4D) CT data are registered between phases before the segmentation is performed on the PVP image. The lesion biomarkers are extracted using data from all phases of enhancement. Finally, classification is performed to determine the types of tumors.

FIG. 4. The correction of abdominal motion (preprocessing) shown on 2D slices of 3D volumes (a) the image before contrast; (b) at PVP; and (c) the noncontrast image after motion correction. Images are shown at the same body location, as seen at the vertebral body. However, the VHL tumor in the right kidney (shown in the highlights) was present only in the enhanced image (b) and not at the same location in image (a). The location of the tumor is corrected in (c) after nonlinear registration.

descriptors. Table I lists the six curvature features used in our HCF method. Additionally, three features based on the gradient magnitude and the CT values from the two phases of enhancement (CT value = HU + 1024) were included in the classification. For each feature, we chose a conservative range and divided it into 98 equally-spaced bins. Voxels whose feature values were outside the range were counted in two additional bins. We concatenated the nine histograms and got a feature vector with 900 dimensions for each lesion.

Due to the large number of features and limited data sample, dimensionality reduction of data by principal component analysis was employed to train the classifier in a lower dimensional space.⁴⁹ Subsequently, the renal data were mapped into a 10D linear subspace according to the distribution of eigenvalues of the covariance matrix. We found experimentally that 10 principal components preserve most of the energy in the PCA data decomposition. The same feature space was used for all the classifications in Fig. 5.

A support vector machine, a set of related supervised learning methods used for classification and regression, was used to perform the classification.⁵⁰ The data were randomly divided into training and test sets with the ratio 1:1 to allow investigating the discriminant power of the sets of features on this small unbalanced dataset. Tumors from one patient were grouped in the same partition. Through random sampling, this

division was repeated 50 times and SVM were trained and tested on each partition. The random sampling method is reminiscent of bootstrapping,⁵¹ but without replacement during the sampling. The SVM kernel was chosen based on Ref. 52. The Library for Support Vector Machines was employed.⁵³

For each random test, SVM resulted in a distance from the decision surface (for classifying two tumor types) and a threshold was swept through these distances to obtain receiver operator characteristic (ROC) curves. A point on the ROC curves was obtained using the average decision value of the 50 tests.

II.E. Statistical analysis

Spearman correlation coefficients between the manual and semi-automated segmentations of lesions were computed and the Wilcoxon paired nonparametric statistical test determined the significance of results. Volumetric overlaps between manual and semi-automated segmentations were computed and Bland–Altman limits of agreement were calculated to present the bias and 95% agreement at ± 1.96 standard deviations.

ROC curves using HCF were compared with those obtained from using solely the mean CT values of lesions at the two enhancement phases. HCF and CT features were computed from the semi-automatic segmentations and the classification done independently for each criterion. The performances of the two classifiers (HCF vs. CT) were compared using ROCKIT (University of Chicago) (Refs. 54 and 55) to assess the

FIG. 5. The cascade of binary classifiers used for renal lesion classification. The number of correctly classified lesions (true positive ratio) that reaches each branch is presented using HCF.

TABLE I. Features used by the HCF descriptor.

	Lower limit	Upper limit
Min curvature	−1	1
Max curvature	−1	1
Mean curvature	−1	1
Gaussian curvature	−1	1
Curvedness	0	1
Shape index	0	1
Gradient magnitude	0	300
CT value noncontrast	0	1500
CT value portal venous enhancement	0	1500

Note: Lower and upper limits are listed for each feature used in the multidimensional histograms. These limits were selected according to the distributions of features. The number of bins used for each feature was 100.

FIG. 6. Segmentation of renal lesions. A VHL cancer was segmented in the PVP image (left), as shown by the semi-automated tumor contour, and the segmentation was propagated to the noncontrast data (right). Before contrast-enhancement the lesion was invisible to the eye, but through spatial registration and segmentation propagation, the cancer can be analyzed at all phases of enhancement.

statistical significance of differences between curves and the areas under the curve (AUC). We selected the operating points with the highest sum of sensitivity and specificity for each curve.

A new lesion of unknown etiology can be labeled by the cascade of binary classifiers in Fig. 5 with a different SVM trained for each classifier.

III. RESULTS

Figure 6 shows an example of multiphase segmentation of tumors. The overlaps, agreements, correlation coefficients and p -values for the comparisons between interobserver manual segmentations from 20 lesions, and between the computer segmentation and each of the observers are presented in Table II. There was no significant difference between the first manual and semi-automated volumetric measurements, while significant differences were found between the second observer and the proposed technique ($p=0.05$), as well as between the two observers ($p=0.01$).

A variety of tumors segmented using the semi-automated technique for quantification and classification of renal cancer are presented in Fig. 7. Figure 8 shows the distribution of SI from random single lesions of each type as an example of morphological feature used for lesion classification. Note, in Fig. 8(a), the SI similarities between two cysts. Figure 8(c) indicates that solid BHD and VHL lesions may be difficult to separate by shape index, as both types of cancers have similar distributions. Solid lesions have a wider variance in the SI distributions than more regularly shaped cysts (SI close to 1). Morphological discrepancies between a cystic

HLRCC cancer, more regular and spherical, and a solid VHL can be seen in Fig. 8(b). Finally, quantifiable differences in the shapes of HPRC vs. HLRCC cancers are presented in Fig. 8(d). In this example, the HPRC and HLRCC lesions mimic the distributions of other types of lesions, but their enhancement and appearance distinguish them from other types of cancers. Using HCF, shape descriptors, such as the shape index, are combined with lesion appearance and enhancement to classify tumors.

Figure 9 shows the ROC curves for classifying renal lesions by HCF and CT values. Table 3 presents statistical results for the binary classifiers in Fig. 5; the sensitivity and specificity of tumor classification are reported using HCF. Malignant and benign groups were separated with very high accuracy and our method was significantly more sensitive than using just CT values ($p<0.01$). VHL/BHD and HPRC/HLRCC cancers were separated with a significant improvement from our method over using only CT values ($p=0.02$). Results from the classification of the four types of cancers using HCF features were superior, but not

FIG. 7. 3D renderings of segmented lesions using the semi-automated technique for renal cancer quantification and classification. A total of 25 random lesions of five types are presented; there are five lesions per row, each from a different patient: From top to bottom, VHL, BHD, cysts, HPRC, and HLRCC cases.

TABLE II. Renal lesion quantification variability.

	Correlation/ p -value	Volume	
		Agreement (cm ³)	Overlap
Observer1—CQ	0.99/0.53	-0.15 ± 1.27	0.81 ± 0.06
Observer2—CQ	0.98/0.05	-0.73 ± 1.32	0.80 ± 0.05
Interobserver	0.98/0.01	-0.93 ± 1.98	0.80 ± 0.06

Note: The columns present the Spearman correlation coefficient/ p -value of the Wilcoxon statistical test, Bland–Altman limits of agreement (bias $\pm$ 95% agreement) between volume and maximum linear size measurements, and the volumetric segmentation overlaps. The rows show the comparisons between each of the two independent observers and the computer quantification (CQ), and the interobserver variability.

FIG. 8. Examples of distribution of shape indexes between types of lesions: (a) two benign cysts; (b) a solid VHL cancer and a cystic HLRCC cancer; (c) two solid lesions: VHL and BHD; and (d) two cystic cancers: HPRC and HLRCC.

significantly different, to the classification based solely on lesions' appearance.

Figure 5 also presents the number of lesions that reached each branch using the HCF-based cascade of binary classifiers.

92.5% of the cysts, 68.1% of the VHL, 81.2% of the BHD, 57.8% of the HPRC, and 85.7% of the HLRCC were correctly classified using the setup in Fig. 5 for the classification of lesions of unknown etiology.

FIG. 9. Classification ROC curves by HCF vs. using only mean multiphase CT values. AUC data are given in Table III.

TABLE III. ROC analysis for the classification of renal lesions.

	AUC-HCF	SE-HCF (%)	SP-HCF (%)	AUC-CT	<i>p</i> -value
Benign vs. malignant	0.98 (0.94; 0.99)	97.60	90.80	0.87 (0.78; 0.93)	<0.01
VHL/BHD vs. HPRC/HLRCC	0.99 (0.94; 1.00)	97.20	95.00	0.90 (0.79; 0.96)	0.02
VHL vs. BHD	0.82 (0.64; 0.93)	87.00	69.20	0.63 (0.41; 0.82)	0.12
HPRC vs. HLRCC	0.84 (0.67; 0.94)	89.50	66.70	0.77 (0.58; 0.90)	0.34

Note: Areas under the curve (AUC), sensitivity (SE) and specificity (SP) values are presented for the ROC curves used to classify renal tumors (Fig. 9). The asymmetric 95% confidence intervals are shown for AUC. *p*-values were computed between comparative ROC curves using HCF or solely mean CT values.

IV. DISCUSSIONS

A method for the semi-automated quantification and classification of renal tumors was presented to assist with tumor clinical management. The method is tailored to the difficult segmentation of variable renal lesions through adapting to the tumor shape and intensity. Through interphase intrapatient registration lesions were quantified from images with insufficient visual information (Fig. 6). Patient motion does not affect our segmentation technique, but small errors in registration may impact the estimation of CT values in the noncontrast phase. The correlations between manual and semi-automatic volume measurements were very high. Additionally, the volumetric overlaps give further indications that the segmentations were accurate, which correlations alone do not guarantee. However, the overlap is influenced by the small size of the lesions in the database.

The size of lesions is not an indicator of malignancy, but a factor determining if the patient should undergo surgery. While our method is as reliable as the manual segmentations, the high variability in the reference standard is a limitation of the evaluation of the quantification method.

The multiphase intensity (CT values) of renal lesions is an established marker for diagnosis and likely represents the most important feature in the classification. Complementarily, HCF utilized the morphological features of lesions in their classification and led to significantly improved results. The shape index in Fig. 8 finds discrepancies between types of lesions, but it is not sufficient for classification due to overlaps between distributions of different types of tumors. Using HCF, these structural differences were combined with lesion appearance and enhancement for a comprehensive statistical description of tumors, which improved the classification of renal lesions.

Five types of renal lesions were analyzed: benign cysts, VHL, BHD, HPRC, and HLRCC. The automated classification of tumors showed significant separation between benign and malignant tumors and allowed the further classification into types of cancer. A new lesion of unknown etiology could be labeled using the cascade of binary classifiers in Fig. 5.

VHL and BHD cancers tended to have more irregular shapes than the other renal lesions. Both VHL and BHD are more solid than other renal neoplasms and enhance faster during contrast agent intake. As expected, cysts exhibited the most regular shapes (Fig. 7). The opaque (darker) appearance with low enhancement of HPRC, HLRCC, and cysts, makes these categories difficult to distinguish with the

naked eye, but were correctly separated by our method. The differentiation between VHL and BHD had the poorest results, as both types of cancer exhibit similar features. The classification of malignant and benign tumors was significantly improved by HCF. HCF results were superior to using just CT values for the separation of each type of cancer (as seen in Fig. 9 and Table III), but the difference between the performances of the two technique was not significant, probably due to the small data sample.

The computational times on a quad core 2.66 GHz processor with 3 GB RAM for the segmentation of lesions varied between 1 and 25 s, and one binary classification contributed an additional 1 s.

The proposed technique was primarily designed to assist with the study of hereditary types of renal cancer carcinoma (RCC). Nevertheless, inherited renal cell cancers belong to the same histological types as the nonhereditary cancers, which are more common in clinical practice. For instance, VHL cancer predispose to clear cell RCC, while BHD patients have an increased risk of chromophobe and oncocytic types of RCC. Alternatively, HPRC and HLRCC cancers carry an increased risk for papillary RCC. Clear cell and chromophobe tumors have more vascularity than papillary tumors. Our clinical tool showed significant improvements over the use of CT values alone in the classification of more vascular and less vascular cancers, which could be valuable for the analysis of difficult cases in typical clinical environments.

The small sample of patients and tumors due to the difficulty in collecting cases is a limitation of this study. Future validations of the technique should also include more types of cancer and correlations with pathology. Pathologic reports were not available for our cases. It is also desirable to perform an independent study, when data become available, for validating this technique before it can be introduced to the clinical practice.

To summarize, the computer-aided clinical tool analyzed imaging biomarkers of renal neoplasms to facilitate their noninvasive classification and clinical management with superior results when the shape of lesions was included in the analysis next to enhancement. A combination of morphology, texture, intensity, and enhancement features was proposed for lesion classification for the first time. Experimental results on a CT dataset of 125 renal lesions showed that our noninvasive classification method was significantly superior in distinguishing cancers from benign lesions to the more typical method based on mean CT values. Cancer types

were further classified into four categories (Birt-Hogg-Dubé syndrome, Von Hippel-Lindau disease, hereditary papillary renal carcinoma, and hereditary leiomyomatosis and renal cell cancer).

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